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Piperidino-Hydrocarbon Compounds as Novel Non-Imidazole Histamine H_3-Receptor Antagonists

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Abstract—In search for novel non-imidazole histamine H_3-receptor antagonists, piperidino-hydrocarbon compounds were synthesized using the known non-imidazole histamine H_3-receptor antagonist FUB 637 (3-phenylpropyl 3-piperidinopropyl ether) as lead structure. Piperidino-alkyl derivatives containing highly flexible side chains (**2**, **4**–**7**) were prepared via *N*-alkylation. Compounds containing unsaturated alkyl groups were synthesized in order to investigate the impact of rigidifying the side chain (**8**–**16**). Terminal alkynes were prepared by alkylation of lithium acetylide-ethylenediamine complex, disubstituted alkynes were synthesized by alkylation of the appropriate acetylene in the presence of *n*-butyllithium-*N*,*N*,*N*',*N*'-tetramethylene-ethylene-diamine complex. The novel compounds were investigated in an in vitro functional assay on the guinea-pig ileum, in which *N*-(7-phenylhept-3-ynyl)-piperidine (**14**) proved to be of good potency in this class ($pA_2 = 7.21$). In an in vivo assay the compounds were additionally screened for their abilities to influence central H_3-histaminergic neuron activity in mice with regard to their oral availabilities and distribution properties. In this screening, *N*-pent-4-ynylpiperidine (**9**) and *N*-hex-5-ynylpiperidine (**10**) proved to be highly potent and orally available histamine H_3-receptor antagonists. The ED_{50} values for **9** and **10** were 1.3 and 1.4 mg/kg po, respectively, which is in the potency range of the reference antagonist thioperamide. © 2002 Published by Elsevier Science Ltd.

Introduction

The histamine H_3 receptor was identified in 1983 as a presynaptically located autoreceptor.[1] Its regulatory effects on the synthesis and release of histamine in the central nervous system (CNS) within the meaning of a negative feedback mechanism[2] as well as its modulatory effects on other neurotransmitter systems[3] were evidenced soon after. Following the cloning of the human histamine H_3 receptor in 1999,[4] efforts were made to disclose species differences, signal transduction pathways, and receptor isoforms.[4,5] Recently, the histamine H_3 receptor was attributed high constitutive activity in vivo, which was shown to be crucial for the regulation of the activity of histaminergic neurons in rats.[6] Apart from the information gained on the molecular and physiological levels, the influence of the histamine H_3 receptor has been associated with a number of pathophysiological conditions mainly affecting the CNS,[7] and potential therapeutic applications for histamine H_3-receptor ligands have been proposed, for example, Alzheimer's disease,[8] memory and learning deficits,[9] and attention-deficit hyperactivity disorder (ADHD).[10]

The physiological and pathophysiological implications of histamine H_3 receptors increase the need for potent and selective ligands as pharmacological tools and potential candidates for drug development. For example, the acetylene derivative GT-2331 (Perceptin™), a highly potent histamine H_3-receptor antagonist ($pA_2 = 8.5$),[11] is currently undergoing clinical trials for the treatment of ADHD. This compound contains a

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cyclopropyl moiety connected to a triple bond thereby increasing the rigidity of the side chain (Fig. 1). GT-2227 ($pA_2 = 7.9$)[11] carries a double bond which may also be regarded as a feature to decrease the flexibility of the hydrocarbon chain compared to the structurally related FUB 427 (4-(6-phenylhexyl)-1*H*-imidazole, $pK_i = 7.1$, $ED_{50} = 1.0$ mg/kg po).[12] All these hydrocarbon compounds contain an imidazole moiety and display high histamine H_3-receptor antagonist potencies.

Recently, the development of non-imidazole histamine H_3-receptor antagonists has been reported.[13] Through imidazole replacement by a piperidino moiety within known antagonists we were able to identify the aliphatic ether derivative FUB 637 ($pA_2 = 8.1$, $ED_{50} = 3.7$ mg/kg po)[14] as a novel lead structure. FUB 637 displays oral in vivo potency and favourable pharmacokinetic properties due to potentially less pronounced interactions with the cytochrome P_{450} enzyme system. In addition, FUB 637 shows high in vitro potency in the same concentration range as that of the reference antagonist ciproxifan.[15,30] However, when the imidazole moiety of the hydrocarbon derivative FUB 427 is replaced by a piperidino group (**3**), antagonist activity decreases significantly (cf. Table 1).[14] This focuses attention on the importance of a polar group and its effect within the side chain as contained in FUB 637. Thus, the nature of the side chain in terms of its electronic properties, flexibility and rigidity is likely to be of great interest in the development of non-imidazole histamine H_3-receptor antagonists of the FUB 637-type.

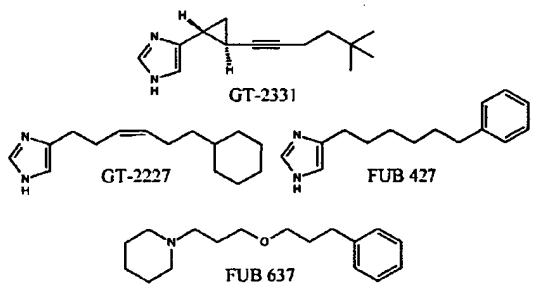
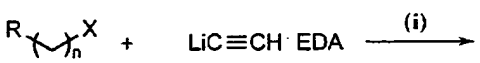
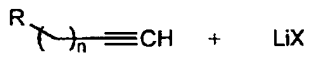


Figure 1. Imidazole and non-imidazole histamine H_3-receptor antagonists.



8a, 9a, 13a, 14a



8, 9, 13b, 14b

Scheme 1. Synthesis of precursors **13b**, **14b** and target compounds **8**, **9**. Legend: (i) tetrahydrofuran or dimethylsulfoxide, rt→45 °C, 24 h, argon; EDA = ethylenediamine; R = piperidino (**8a**, **9a**, **8**, **9**), R = phenyl (**13a/b**, **14a/b**), n = 2 (**8a**, **8**, **13a/b**), n = 3 (**9a**, **9**, **14a/b**). Please refer to Experimental for exceptions concerning **13b**.

In order to investigate the effect of increased flexibility of the side chain on antagonist potency, the polar group was removed to give pure alkyl derivatives of various chain lengths in the present study. Furthermore, the polar ether group was replaced by double and triple bonds, respectively, as a means of stiffening the side chain. In addition, structure–activity relationships (SAR) resulting from variation of the position of the triple bond between the piperidino and lipophilic moieties are discussed. In order to extend our work in the non-imidazole field we introduce here a piperidino-hydrocarbon class of histamine H_3-receptor antagonists which in contrast to FUB 637 is without a polar group.

Results and Discussion

Chemistry

The alkyl derivatives **2** and **4–7** were prepared by *N*-alkylation under basic conditions in the presence of catalytic amounts of KI starting from piperidine and the corresponding commercially available 1-haloalkanes or 1-halo-ω-phenylalkanes. Alkyne **10** was synthesized using the same method.

The mono-substituted alkynes were prepared from lithium acetylide-ethylenediamine (EDA) complex which was reacted with the appropriate 1-halo-ω-phenylalkane (**13b**, **14b**), 1-(2-chloroethyl)piperidine (**8**), or 1-(3-methylsulfonylpropyl)piperidine (**9**) (Scheme 1).[16] Reaction temperature was assured to not exceed 45 °C in order to minimize decomposition of the complex during the reaction period.[17] For precursor **13b**, which was derived from 1-iodo-2-phenylethane, temperatures were maintained as low as possible to avoid elimination. In general, yields were satisfactory with no difference observed when either dimethylsulfoxide or tetrahydrofuran were used as solvents.

Alkylation of the mono-substituted alkynes was achieved by formation of the carbanion of **13b** or **14b**, respectively, using *n*-butyllithium-*N*,*N*,*N*′,*N*′-tetramethylene-ethylenediamine (*n*-BuLi-TMEDA) complex generated at 0 °C, followed by addition of the alkyne in dry tetrahydrofuran at −20 °C.[18] Yields ranged from 4 to 62%, with phenylacetylene derivatives (**11**, **15**) generally giving lower yields (Scheme 2).

Target compound **12** was obtained in good yield through stereoselective reduction of the triple bond of **13** with $LiAlH_4$.[19] While no reduction was observed when the reaction was carried out in refluxing tetrahydrofuran, **13** was stereoselectively reduced in refluxing diglyme to give product **12** containing the *E*-configured alkene only (based on NMR-data).

Pharmacology

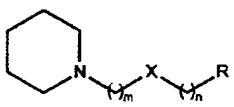
The novel compounds were investigated in vitro for their abilities to antagonize histamine H_3-receptor mediated relaxation in the field-stimulated guinea-pig ileum longitudinal muscle preparation. In order to

assure a histamine H_3-receptor mediated effect in this model, compounds needed to be screened for their potencies at muscarinic M_3 receptors previous to H_3-receptor testing (Table 1). In vivo the level of the main metabolite of histamine, N^{τ}-methylhistamine, was measured in the cerebral cortex of mice after oral administration. A histamine H_3-receptor antagonist blocks the physiological negative-feed back loop mediated by presynaptic H_3 receptors and thereby increases histaminergic neuron activity.

In the phenylalkyl series, the butyl derivative **1** displays weak antagonist activity in vitro, while the next higher homologues **2** and **3**, respectively, show increased potency in vitro (Table 1). Based on this trend, further elongation of the alkyl chain was expected to further increase antagonist potency. Interestingly, however, chain elongation (**4**, **6**, **7**) was accompanied by an increase in antagonist activity at muscarinic M_3 receptors in vitro (pA_2 (M_3):[20] 6.86±0.03 (**4**), 6.89±0.03 (**6**), 6.91±0.04 (**7**)). As a consequence, histamine H_3-receptor antagonist potency was not determinable in these cases as the affinity for muscarinic M_3 receptors interferes with the expected histamine H_3-receptor potency, a well-known dilemma in functional organ bath studies of this type. Yet these studies serve as valuable tools since functionality, external conditions, and the consideration of the whole organ reflect physiological parameters. In addition, compounds **4**, **6**, and **7** display no detectable effects in vivo. Contrary to this finding, the pure alkyl derivative **5** shows low in vitro and moderate in vivo potency.

As for the non-phenyl derivative **5**, the mono-substituted alkyne derivatives **8**, **9**, and **10** also display moderate in vitro potencies. In this series a gradual increase in in vitro potency is observed as the length of the spacer between the piperidino and terminal alkynyl moieties increases. Compounds **9** and **10** surprisingly display good oral potencies in vivo comparable to the reference antagonist thioperamide and surpassing the antagonist activity of the lead compound FUB 637. The antagonist activities of **9** and **10** in vitro are however relatively low. Previously, FUB 465 has been described to act as an inverse agonist at the constitutively active histamine H_3 receptor after oral administration to mice.[6] While FUB 465 displayed antagonist in vitro potency in the micromolar concentration range on the rat synaptosomal [^{3}H]-histamine release model, the enhancement of the N^{τ}-methylhistamine level, a reliable measure of histaminergic neuron activity in vivo,[21] resulted in relatively high in vivo potency.[6] The observation that the increase in N^{τ}-methylhistamine level is not always well correlated with the compound's potency as an antagonist was also made by others.[22,23] As a consequence, the high in vivo potencies of compounds **9**

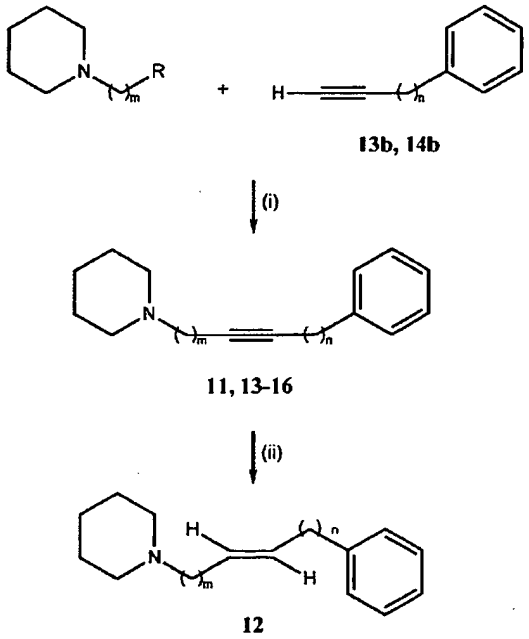
Table 1. Chemical structures and antagonist potencies of novel non-imidazole hydrocarbon-type histamine H_3-receptor antagonists



No.	m	X	n	R	pA_2 (M_3)±SEM[a]	pA_2 (H_3)±SEM[b]	ED_{50}±SEM[c] (mg/kg) po
1	3	$-CH_2$	0	Ph		5.7[d]	20[d]
2	4	$-CH_2-$	0	Ph	5.60±0.07	6.38±0.04	≥30
3	5	$-CH_2-$	0	Ph		6.5[d]	>10[d]
4	6	$-CH_2$	0	Ph	6.86±0.03	n.d.[e]	>10
5	6	$-CH_2-$	0	CH_3	5.60±0.07	5.71±0.05	16±3
6	7	$-CH_2-$	0	Ph	6.89±0.03	n.d.[e]	>10
7	8	$-CH_2$	0	Ph	6.91±0.04	n.d.[e]	>10
8	2	C≡C—	0	H	4.24±0.11	5.38±0.10	≥10
9	3	—C≡C—	0	H	3.93±0.02	5.69±0.06	1.3±0.5
10	4	—C≡C—	0	H	4.70±0.10	6.16±0.05	1.4±0.5
11	2	—C≡C—	0	Ph	4.97±0.07	6.47±0.04	10
12	2	—CH=CH—	2	Ph	5.80±0.02	6.66±0.08	10
13	2	—C≡C—	2	Ph	5.40±0.03	6.78±0.08	>10
14	2	—C≡C—	3	Ph	6.01±0.04	7.21±0.09	>10
15	3	—C≡C—	0	Ph	5.08±0.05	6.42±0.06	30
16	3	—C≡C	2	Ph	5.44±0.04	6.91±0.11	15±5
FUB 637	3	O	3	Ph		8.1[d]	3.7±1[d]
FUB 427						7.1[f]	1.0±0.3[f]
GT-2227						7.9±0.1[g]	
GT-2331						8.5±0.03[g]	
Ciproxifan						8.4[h]	0.14±0.03[h]
Thioperamide						8.3[i]	1.0±0.5[h]

[a]Functional M_3-receptor in vitro assay on guinea-pig ileum.[20]
[b]Functional H_3-receptor in vitro assay on guinea-pig ileum.[26,27]
[c]Central H_3-receptor assay after po administration to mice.[28]
[d]ref 14.
[e]n.d., not determinable due to relatively high potency at muscarinic M_3 receptors.
[f]ref 12.
[g]ref 11.
[h]ref 30.
[i]ref 32.

and **10** in this study are likely due to their inverse agonist rather than (neutral) antagonist potency. Furthermore, the difference between the in vivo and in vitro potencies of **9** and **10** may be attributed to species differences, or significant improvement in absorption, or in distribution into the CNS. In addition, under in vivo conditions the formation of active metabolites or the involvement of other receptor systems which might influence the in vivo effect cannot be excluded and require further investigation.



Scheme 2. Synthesis of final compounds **11–16**. m = 2, R = Cl; m = 3, R = OSO_2CH_3. Legend: (i) *n*-BuLi (1.6 M), TMEDA, argon, 55 °C, 24 h; (ii) $LiAlH_4$, diglyme, 0 °C→reflux, 8 h; m = 2 (**11**–**14**), m = 3 (**15**, **16**); n = 0 (**11**, **15**), n = 2 (**12**, **13**, **16**), n = 3 (**14**).

The terminal alkynyl moiety of **8** was substituted with a phenyl group to give compound **11** which displays higher in vitro potency than the mono-substituted analogue **8** and moderate in vivo potency. Also derived from **8**, introduction of an alkyl spacer between the unsaturated functional group and the lipophilic phenyl moiety results in increased in vitro potencies of the *E*-configured alkene derivative **12** and its alkynyl analogue **13**. Further elongation of the spacer leads to **14**, the most potent histamine H_3-receptor antagonist in vitro in this series. In vivo, the influence of the spacer is less marked. While **12** displays moderate in vivo potency, no effect on the N^{τ}-methylhistamine level was observed for **13** and **14**. Elongation of the first spacer slightly decreases in vitro potency (**15**, **16**) compared to **14**, but at the same time slightly exerts beneficial effects on the antagonist activity in vivo.

Conclusion

Novel hydrocarbon non-imidazole histamine H_3-receptor antagonists derived from FUB 637, have been prepared possessing either a highly flexible alkyl side chain or linker, respectively, or an unsaturated alkenyl or alkynyl group resulting in increased rigidity of these compounds. Investigation of the compounds in an in vitro functional assay on the guinea-pig ileum led to the identification of *N*-(7-phenylhept-3-ynyl)piperidine (**14**) as the most potent compound in vitro in this series ($pA_2 = 7.21$). Additionally, compounds were investigated for their effects on central histaminergic neuron activity in vivo in mice. In this screening, *N*-pent-4-ynylpiperidine (**9**) and *N*-hex-5-ynylpiperidine (**10**) proved to be orally available histamine H_3-receptor antagonists of good potency ($ED_{50} = 1.3$ and 1.4 mg/kg po) comparable to the antagonist activity of the reference antagonist thioperamide. As an attempt to identify new non-imidazole histamine H_3-receptor antagonists, this novel class of compounds represents an interesting subject for further investigation and development.

Table 2. Physical properties and elemental analysis of hydrocarbon derivatives **1–16**

No.	Formula	M_w (g/mol)	mp (°C)	calcd (%)			found (%)		
				C	H	N	C	H	N
1[a]	$C_{15}H_{23}N{\cdot}C_2H_2O_4$	307.4	150	66.43	8.20	4.56	66.40	8.13	4.61
2	$C_{16}H_{25}N{\cdot}C_2H_2O_4$	321.4	151.9	67.26	8.47	4.36	67.00	8.43	4.52
3[a]	$C_{17}H_{27}N{\cdot}C_2H_2O_4$	335.4	152	68.03	8.71	4.18	68.00	8.76	4.05
4	$C_{18}H_{29}N{\cdot}1.5C_2H_2O_4$	394.5	113.6	63.94	8.18	3.55	63.79	8.08	3.53
5	$C_{13}H_{27}N{\cdot}C_2H_2O_4$	287.4	121.1	62.69	10.17	4.87	62.47	10.03	4.69
6	$C_{19}H_{31}N{\cdot}C_2H_2O_4$	363.5	135.7	69.39	9.15	3.85	69.41	8.96	3.78
7	$C_{20}H_{33}N{\cdot}C_2H_2O_4$	377.5	123.8	69.99	9.34	3.71	69.98	9.16	3.60
8	$C_9H_{15}N{\cdot}C_2H_2O_4$	227.3	152.2	58.14	7.54	6.16	57.97	7.29	6.09
9	$C_{10}H_{17}N{\cdot}C_2H_2O_4{\cdot}0.25H_2O$	245.8	145.1	58.64	7.99	5.69	58.89	7.84	5.88
10	$C_{11}H_{19}N{\cdot}C_2H_2O_4$	255.3	145.2	61.16	8.29	5.49	60.81	8.26	5.38
11	$C_{15}H_{19}N{\cdot}C_2H_2O_4{\cdot}0.25H_2O$	307.9	144.3	66.32	7.04	4.55	66.04	6.95	4.48
12	$C_{17}H_{25}N{\cdot}C_2H_2O_4$	333.4	154.3	68.44	8.16	4.20	68.23	8.19	4.08
13	$C_{17}H_{23}N{\cdot}C_2H_2O_4{\cdot}1H_2O$	349.4	131.2	65.31	7.79	4.01	65.39	7.52	4.37
14	$C_{18}H_{25}N{\cdot}C_2H_2O_4$	345.4	108.6	69.54	7.88	4.05	66.52	7.50	4.21
15	$C_{15}H_{19}N{\cdot}C_2H_2O_4{\cdot}0.25H_2O$	321.9	176.9	67.17	7.35	4.35	66.84	7.06	4.19
16	$C_{18}H_{25}N{\cdot}C_2H_2O_4$	345.4	128.4	69.54	7.88	4.05	69.52	8.04	4.06

[a]ref 14.

Experimental

Chemistry

General procedures. Melting points were determined on an Electrothermal IA 9000 digital or a Büchi 512 apparatus. NMR spectra were recorded on a Bruker DPX 400 Avance spectrometer (^{1}H: 400 MHz, ^{13}C 100 MHz). ^{1}H NMR chemical shifts are expressed in ppm downfield from internal tetramethylsilane as reference. Data are reported in the following order: multiplicity (br, broad; dt, doublet of a triplet; t, triplet; td, triplet of a doublet; m, multiplet; H_a, axial proton; H_e, equatorial proton; Pip, piperidino; Ph, phenyl), number of protons, and approximate coupling constants in hertz (Hz). ^{13}C NMR data are expressed as chemical shifts downfield (Ox, oxalic acid). Mass spectra were obtained on Finnigan MAT CH7A (EI–MS), Finnigan MAT CH5DF (FAB-MS), and Finnigan MAT 711 (high-resolution mass spectra), spectrometer resolving power 12 500. IR spectra were recorded on a 1420 Ratio-Recording or a 297 spectral photometer (Perkin–Elmer) in KBr (m, medium; s, strong). Elemental analyses (C, H, N) for all compounds were measured on Perkin–Elmer 240 B or Perkin–Elmer 240 C instruments and are within 0.4% of theoretical values unless otherwise stated (Table 2).

General procedure for the preparation of alkanes 2, 4–7, and alkyne 10

A solution of the desired 1-chloro-ω-phenylalkane (**2**, **4**, **6**, **7**), 4-chlorobutyne (**10**), or 1-bromooctane (**5**) (1 equiv), K_2CO_3 (2.4 equiv), piperidine (1.2 equiv), and a catalytic amount of KI in acetonitrile (5 mL/mmol of piperidine) (except **10**: acetone) was refluxed for 12–18 h. The mixture was filtered and the solvent removed under reduced pressure. Unless otherwise stated, the work up procedure was performed as follows: The oily residue was suspended in water, aqueous HCl (2 M) was added until a pH value of approximately 1 was reached. The mixture was extracted with dichloromethane. NaOH (2 M) was added to the aqueous layer, and the mixture was brought to a pH of approximately 10 and extracted with dichloromethane. The organic layers were combined, dried (Na_2SO_4), and the solvent removed under reduced pressure to give yellow or orange oils.

***N*-(5-Phenylpentyl)piperidine hydrogen oxalate (2).** The final product was crystallized as a salt of oxalic acid from isopropanol (72%). ^{1}H NMR (CF_3COOD) 1.63–1.71 (m, 2H, PipN-$(CH_2)_2CH_2$), 1.73–1.83 (m, 1H, Pip-4H_a), 1.92–1.98 (m, 2H, $PhCH_2CH_2$), 2.01–2.12 (m, 4H, Pip-3,5H_a, PipN-CH_2CH_2), 2.17–2.21 (m, 1H, Pip-4H_e), 2.25–2.29 (m, 2H, Pip-3,5H_e), 2.88–2.91 (t, J=7.4 Hz, 2H, $PhCH_2$), 3.10–3.18 (m, 2H, Pip-2,6H_a), 3.32–3.37 (m, 2H, PipN-CH_2), 3.84–3.87 (m, 2H, Pip-2,6H_e), 6.71 (br, 1H, NH^+), 7.39–7.41 (m, 3H, Ph-2,4,6H), 7.48–7.52 (m, 2H, Ph-3,5H); EI–MS (70 eV) m/z (%) 231 (M^+, 5).

***N*-(7-Phenylheptyl)piperidine hydrogen oxalate (4).** The final product was crystallized as a salt of oxalic acid from isopropanol/diethyl ether (4%). ^{1}H NMR (CF_3COOD) 1.45 (m, 6H, PipN-$(CH_2)_2(CH_2)_3$), 1.58–1.62 (m, 1H, Pip-4H_a), 1.66–1.73 (m, 2H, $PhCH_2CH_2$), 1.82 (m, 2H, PipN-CH_2CH_2), 1.88–1.95 (m, 2H, Pip-3,5H_a), 1.99–2.03 (m, 1H, Pip-4H_e), 2.07–2.12 (m, 2H, Pip-3,5H_e), 2.64–2.68 (t, J=7.6 Hz, 2H, $PhCH_2$), 2.93–3.01 (m, 2H, Pip-2,6H_a), 3.14–3.19 (m, 2H, PipN-CH_2), 3.67–3.71 (m, 2H, Pip-2,6H_e), 6.55 (br, 1H, NH^+), 7.16–7.22 (m, 3H, Ph-2,4,6H), 7.27–7.31 (m, 2H, Ph-3,5H); EI–MS (70 eV) m/z (%) 259 (M^+, 3).

***N*-Octylpiperidine hydrogen oxalate (5).** The final product was crystallized as a salt of oxalic acid from isopropanol (75%). ^{1}H NMR (d_6-DMSO) 0.84–0.88 (t, J=6.8 Hz, 3H, CH_3), 1.26 (br, 10H, $Ph(CH_2)_2(CH_2)_5$), 1.51–1.61 (m, 4H, Pip-3,5H_a, Pip-4H_2), 1.69–1.72 (m, 4H, Pip-NCH_2CH_2, Pip-3,5H_e), 2.90–2.94 (m, 2H, Pip-2,6H_a), 3.06 (br, 4H, Pip-NCH_2, Pip-2,6H_e); EI–MS (70 eV) m/z (%) 197 (M^+, 3).

***N*-(8-Phenyloctyl)piperidine hydrogen oxalate (6).** The final product was crystallized as a salt of oxalic acid from isopropanol (73%). ^{1}H NMR (CF_3COOD) δ 1.42 (m, 8H, PipN-$(CH_2)_2(CH_2)_4$), 1.55–1.61 (m, 1H, Pip-4H_a), 1.68 (m, 2H, $PhCH_2CH_2$), 1.82–1.84 (m, 2H, PipN-CH_2CH_2), 1.88–1.94 (m, 2H, Pip-3,5H_a), 1.98–2.01 (m, 1H, Pip-4H_e), 2.07–2.11 (m, 2H, Pip-3,5H_e), 2.63–2.67 (t, J=7.6 Hz, 2H, $PhCH_2$), 2.93–3.01 (m, 2H, Pip-2,6H_a), 3.14–3.20 (m, 2H, PipN-CH_2), 3.68–3.71 (m, 2H, Pip-2,6H_e), 6.55 (br, 1H, NH^+), 7.15–7.23 (m, 3H, Ph-2,4,6H), 7.27–7.30 (m, 2H, Ph-3,5H); EI–MS (70 eV) m/z (%) 273 (M^+, 4).

***N*-(9-Phenylnonyl)piperidine hydrogen oxalate (7).** The final product was crystallized as a salt of oxalic acid from isopropanol (62%). ^{1}H NMR (d_6-DMSO) 1.25 (br, 10H, $Ph(CH_2)_2(CH_2)_5$), 1.54–1.59 (m, 6H, $PhCH_2CH_2$, Pip-3,5H_a, Pip-4H_2), 1.69–1.72 (m, 4H, Pip-NCH_2CH_2, Pip-3,5H_e), 2.54–2.58 (t, J=7.6 Hz, 2H, $PhCH_2$), 2.90–2.94 (m, 2H, Pip-2,6H_a), 3.06 (br, 4H, Pip-NCH_2, Pip-2,6H_e), 7.14–7.18 (m, 3H, Ph-2,4,6H), 7.25–7.28 (m, 2H, Ph-3,5H); EI–MS (70 eV) m/z (%) 287 (M^+, 3).

***N*-Hex-5-ynylpiperidine hydrogen oxalate (10).** After filtration, the residue was further purified through column chromatography, using dichloromethane/methanol 95:5+0.5% aqueous NH_3 as eluent. The final product was crystallized as a salt of oxalic acid from ethanol/diethyl ether (39%). ^{1}H NMR (CF_3COOD) δ 1.57–1.71 (m, 3H, $CH_2CH_2C{\equiv}$, Pip-4H_a), 1.86–1.94 (m, 2H, Pip-3,5H_a), 1.97–2.04 (m, 3H, Pip-4H_e, PipN-CH_2CH_2), 2.06 (t, J=2.4 Hz, 1H, ≡CH), 2.10–2.14 (m, 2H, Pip-3,5H_a), 2.31–2.36 (dt, J=2.4 Hz and J=6.5 Hz, 2H, $CH_2C{\equiv}$), 2.98–3.07 (m, 2H, Pip-2,6H_a), 3.24–3.29 (m, 2H, PipN-CH_2), 3.73–3.77 (m, 2H, Pip-2,6H_e), 6.66 (br, 1H, NH^+); ^{13}C NMR (CF_3COOD) δ 18.9 ($CH_2C{\equiv}$), 23.2 (Pip-4), 25.1 (PipN-CH_2CH_2), 25.2 (Pip-3,5), 26.5 ($CH_2CH_2C{\equiv}$), 56.9 (Pip-2,6), 60.1 (PipN-CH_2), 71.4 (≡CH), 84.8 ($C{\equiv}$CH), 162.8 (Ox); EI–MS m/z (%) 165 (M^+, 3); IR (cm^{-1}) 3214s (ν[≡C-H]).

General procedure for the preparation of alkynes 13b, 14b, 8, and 9

A 100 mL, three-necked flask was dried, flushed with argon and charged with lithium-acetylenide-EDA complex (1.1 equiv, except **8**: 2.2 equiv) via argon coun-

ter current. Dry tetrahydrofuran (except **8**: dimethylsulfoxide) was added to make the resulting suspension approximately 2 M in complex. A 1 M solution of the desired halide (1 equiv) was then added over a period of 30 min at room temperature (except **13b**: at 0 °C). After the addition was completed the mixture was brought to 45 °C for 24 h (except **13b** which was held at 0 °C for 2 h, was then allowed to warm up to room temperature and stirred for 3 h). Water was carefully added to the reaction mixture. The aqueous layer was extracted with ethyl acetate, the organic layers were combined, dried ($MgSO_4$) and the solvent was removed under reduced pressure. The residue was further purified through column chromatography using dichloromethane/methanol 99:1 as eluent unless otherwise stated.

But-3-ynylbenzene (13b).[24] Yield: 10%; ^{1}H NMR ($CDCl_3$) δ 1.99 (t, J = 2.5 Hz, 1H, ≡C*H*), 2.62–2.78 (m, 4H, Ph(CH_2)$_2$), 7.13–7.21 (m, 3H, Ph-2,4,6*H*), 7.27–7.31 (m, 2H, Ph-3,5*H*); EI–MS (70 eV) *m/z* (%) 130 (M^+, 23).

Pent-4-ynylbenzene (14b).[25] Yield: 30%; ^{1}H NMR ($CDCl_3$) δ 1.81–1.88 (m, 2H, PhCH$_2$CH_2), 1.98 (t, J = 2.6 Hz, 1H, ≡C*H*), 2.18–2.22 (dt, J = 7.0 and 2.6 Hz, 2H, Ph(CH$_2$)$_2$CH_2), 2.74 (t, J = 7.6 Hz, 2H, PhCH_2), 7.11–7.20 (m, 3H, Ph-2,4,6*H*), 7.25–7.30 (m, 2H, Ph-3,5*H*); EI–MS (70 eV) *m/z* (%) 144 (M^+, 40).

***N*-But-3-ynylpiperidine hydrogen oxalate (8).** 1-(2-Chloroethyl)piperidine hydrochloride was used as starting material. The reaction was carried out in dry dimethylsulfoxide. Dichloromethane/methanol 95:5 + 0.5% aqueous NH_3 was used as eluent. The final product was crystallized as a salt of oxalic acid from ethanol/diethyl ether (28%). ^{1}H NMR (d_6-DMSO) δ 1.49 (m, 2H, Pip-4H_2), 1.66–1.70 (m, 4H, Pip-3,5H_2), 2.59–2.63 (dt, 2H, J = 2.5 Hz, J = 7.7 Hz, CH_2≡C), 3.01 (t, J = 2.5 Hz, 1H, ≡C-*H*), 3.06–3.1 (m, 6H, Pip-2,6H_2, PipN-CH_2); ^{13}C NMR (CF_3COOD) δ 14.2 (≡C*C*H$_2$), 23.1 (Pip-4), 25.2 (Pip-3,5), 53.9 (Pip-2,6), 55.7 (PipN-*C*H$_2$), 64.5 (≡*C*-H), 90.1 (*C*≡C-H), 160.3 (Ox); FAB$^+$-MS *m/z* (%) 138 ($M-H^+$, 100); IR (cm^{-1}) 3216m (ν[≡C-H]), 2250m (ν[C≡C]).

***N*-Pent-4-ynylpiperidine hydrogen oxalate (9).** Dichloromethane/methanol 90:10 + 1% aqueous NH_3 was used as eluent. The final product was crystallized as a salt of oxalic acid from ethanol/diethyl ether (10%). ^{1}H NMR (CF_3COOD) δ 1.51–1.69 (m, 1H, Pip-4H_a), 1.86–1.97 (m, 2H, Pip-3,5H_a), 2.00–2.15 (m, 5H, Pip-4H_e, Pip-3,5H_e, PipN-CH$_2$CH_2), 2.16–2.18 (t, J = 2.6 Hz, 1H, ≡C-*H*), 2.32–2.47 (m, 2H, CH_2≡C), 2.99–3.08 (m, 2H, Pip-2,6H_a), 3.38–3.43 (m, 2H, PipN-CH_2), 3.77–3.81 (m, 2H, Pip-2,6H_e), 6.77 (br, 1H, NH^+); ^{13}C NMR (CF_3COOD) δ 17.1 (≡C*C*H$_2$), 23.1 (Pip-4), 24.2 (PipN-CH$_2$*C*H$_2$), 25.2 (Pip-3,5), 57.1 (Pip-2,6), 60.2 (PipN-*C*H$_2$), 72.7 (≡*C*-H), 83.0 (*C*≡C-H), 162.3 (Ox); FAB$^+$-MS *m/z* (%) 152 ($M-H^+$, 100); IR (cm^{-1}) 3221s (ν[≡C-H]).

General procedure for the preparation of alkynes 11 and 13–16

At 0 °C, *n*-BuLi (1.6 M, 1.3 equiv) was added to TMEDA (1.3 equiv) and stirred for 30 min. The reaction mixture was cooled to −20 °C and a 1 M solution of the appropriate alkyne (1 equiv) in dry tetrahydrofuran was added. The mixture was stirred for 60 min. 1-(2-Chloroethyl)piperidine (**11**, **13**, **14**; 1-(2-chloroethyl)piperidine hydrochloride) was used as educt. The base was liberated separately in an additional reaction vessel with *n*-BuLi, 1.6 M) or 1-(3-methylsulfonylpropyl)piperidine (**15**, **16**) (1.5 equiv) was added and the temperature was raised to 55 °C for 24 h. The reaction mixture was treated with water, extracted with ethyl acetate, dried ($MgSO_4$), and the solvent was removed under reduced pressure. Further purification was performed as stated for each individual compound.

***N*-(4-Phenylbut-3-ynyl)piperidine hydrogen oxalate (11).** Synthesized from commercially available phenylacetylene and 1-(2-chloroethyl)piperidine. The crude product was purified through column chromatography (eluent: dichloromethane/methanol 95:5 + 0.5% aqueous NH_3). The final product was crystallized as a salt of oxalic acid from ethanol/diethyl ether, and recrystallized from ethanol (4%). ^{1}H NMR (CF_3COOD) δ 1.63–1.72 (m, 1H, Pip-4H_a), 1.91–2.05 (m, 3H, Pip-4H_e, Pip-3,5H_a), 2.14–2.18 (m, 2H, Pip-3,5H_e), 3.04–3.07 (t, J = 6.4 Hz, 2H, PhCH_2), 3.12–3.20 (m, 2H, Pip-2,6H_a), 3.46–3.51 (m, 2H, PipN-CH_2), 3.84–3.87 (m, 2H, Pip-2,6H_e), 6.66 (br, 1H, NH^+), 7.32–7.44 (m, 5H, Ph-2,3,4,5,6*H*); ^{13}C NMR (CF_3COOD) δ 17.2 (≡C*C*H$_2$), 23.1 (Pip-4), 25.0 (Pip-3,5), 56.8 (Pip-2,6), 58.0 (PipN-*C*H$_2$), 81.9 (≡C...Ph), 87.8 (≡C...Pip), 123.6 (Ph-1), 130.5 (Ph-4), 131.3 (Ph-2,3,5,6), 162.3 (Ox); FAB$^+$-MS *m/z* (%) 214 (M-H$^+$, 100).

***(E)*-*N*-(6-Phenylhex-3-enyl)piperidine hydrogen oxalate (12).** $LiAlH_4$ (5 mmol, 0.2 g) was suspended in diglyme (15 mL). **13** (2.5 mmol, 0.6 g) was added at 0 °C and the mixture was refluxed for 8 h. After the reaction was completed, saturated $NaKC_4H_6O_6$ solution (Seignette's solution) was added at 0 °C, and the mixture was filtered. The precipitate was washed thoroughly with hot ethyl acetate. The filtrate was extracted three times with ethyl acetate, all organic layers were combined, dried ($MgSO_4$), and the solvent was evaporated under reduced pressure. The crude product was purified by column chromatography (eluent: dichloromethane/methanol 90:10 + 1% aqueous NH_3) and the final product crystallized as a salt of oxalic acid from ethanol/diethyl ether (44%). ^{1}H NMR (CF_3COOD) δ 1.52–1.62 (m, 1H, Pip-4H_a), 1.69–1.79 (m, 2H, Pip-3,5H_a), 1.91–1.94 (m, 1H, Pip-4H_e), 2.00–2.04 (m, 2H, Pip-3,5H_e), 2.46–2.54 (m, 4H, CH_2CH=CHCH_2), 2.76–2.80 (t, J = 7.2 Hz, 2H, PhCH_2), 2.87–2.96 (m, 2H, Pip-2,6H_a), 3.13–3.18 (m, 2H, PipN-CH_2), 3.55–3.58 (m, 2H, Pip-2,6H_e), 5.32–5.39 (td, J = 15.4 and 6.6 Hz, 1H, Ph...C*H*=), 5.73–5.79 (td, J = 15.4 and 6.9 Hz, 1H, PipN...C*H*=), 5.92 (br, 1H, NH^+), 7.20–7.22 (m, 3H, Ph-2,4,6*H*), 7.30–7.33 (m, 2H, Ph-3,5*H*), no signals were observed for the related *Z*-configured isomer; ^{13}C NMR (CF_3COOD) δ 22.9 (Pip-4), 24.9 (Pip-3,5), 29.3 (=CHCH$_2$...Ph), 35.1 (=CHCH_2...Pip), 36.6 (PhCH_2), 56.6 (Pip-2,6), 59.4 (PipN-*C*H$_2$), 124.8 (Ph....*C*H=), 128.0 (Ph-4), 130.4 (Ph-2,3,5,6), 139 (PipN...*C*H=), 143.7 (Ph-1), 162.3 (Ox); FAB$^+$-MS *m/z* (%) 244 ($M-H^+$, 100).

N-(6-Phenylhex-3-ynyl)piperidine hydrogen oxalate (13). Synthesized from **13b** and 1-(2-chloroethyl)piperidine. The crude product was purified through flash column chromatography (eluent: diethyl ether/petroleum ether/triethylamine 66:33:1). The final product was crystallized as a salt of oxalic acid from ethanol/diethyl ether and recrystallized from ethanol (36%). ^{1}H NMR (CF_3COOD) δ 1.49–1.68 (m, 3H, Pip-4H_a, Pip-3,5H_a), 1.88–1.92 (m, 1H, Pip-4H_e), 1.96–1.99 (m, 2H, Pip-3,5H_e), 2.59–2.63 (m, 2H, ≡CCH_2...Ph), 2.70–2.74 (m, 2H, ≡CCH_2...Pip), 2.86–2.93 (m, 4H, Pip-2,6H_a, PhCH_2), 3.19–3.23 (t, J = 6.3 Hz, 2H, PipN-CH_2), 3.48–3.52 (m, 2H, Pip-2,6H_e), 5.77 (br, 1H, NH^+), 7.27–7.30 (m, 3H, Ph-2,4,6H), 7.36–7.39 (m, 2H, Ph-3,5H); ^{13}C NMR (CF_3COOD) δ 16.7 (≡CCH_2...Pip), 21.4 (≡CCH_2...Ph), 22.9 (Pip-4), 25.1 (Pip-3,5), 35.9 (PhCH_2), 56.5 (Pip-2,6), 57.8 (PipN-CH_2), 74.8 (Ph...C≡), 88.1 (Pip...C≡), 128.6 (Ph-4), 130.5 (Ph-2,3,5,6), 142.9 (Ph-1), 162.3 (Ox); FAB$^+$-MS m/z (%) 242 (M−H$^+$, 100).

N-(7-Phenylhept-3-ynyl)piperidine hydrogen oxalate (14). Synthesized from **14b** and 1-(2-chloroethyl)piperidine. The oily residue was suspended in water, aqueous HCl (1 M) was added (pH ~ 1) and the mixture was extracted with ethyl acetate. NaOH (2 M) was added to the aqueous layer (pH > 10) which was extracted with ethyl acetate. The organic layers were combined, dried ($MgSO_4$), and the solvent removed under reduced pressure. The final product was crystallized as a salt of oxalic acid from ethanol/diethyl ether (62%). ^{1}H NMR (CF_3COOD) δ 1.59–1.69 (m, 1H, Pip-4H_a), 1.86–1.96 (m, 4H, $PhCH_2CH_2$, Pip-3,5H_a), 1.99–2.01 (m, 1H, Pip-4H_e), 2.10–2.14 (m, 2H, Pip-3,5H_e), 2.21–2.25 (m, 2H, Ph...CH_2C≡), 2.73–2.77 (t, J = 7.5 Hz, 2H, PhCH_2), 2.78–2.80 (m, 2H, Pip...CH_2C≡), 3.04–3.12 (m, 2H, Pip-2,6H_a), 3.31–3.36 (m, 2H, PipN-CH_2), 3.76–3.79 (m, 2H, Pip-2,6H_e), 6.39 (br, 1H, NH^+), 7.20–7.22 (m, 3H, Ph-2,4,6H), 7.28–7.32 (m, 2H, Ph-3,5H); ^{13}C NMR (CF_3COOD) δ 16.7 (≡CCH_2...Pip), 19.4 (≡CCH_2...Ph), 23.1 (Pip-4), 25.2 (Pip-3,5), 31.8 ($PhCH_2CH_2$), 36.7 (PhCH_2), 56.7 (Pip-2,6), 58.0 (PipN-CH_2), 73.8 (Ph...C≡), 88.4 (Pip...C≡), 128.0 (Ph-4), 130.4 (Ph-2,3,5,6), 143.7 (Ph-1), 162.4 (Ox); FAB$^+$-MS m/z (%) 256 (M−H$^+$, 83); HRMS (80 eV) calcd 255.19858, found 255.19870. Anal. ($C_{18}H_{25}N{\cdot}C_2H_2O_4$) C: calcd, 69.54, found 66.52; H, N.

N-(5-Phenylpent-4-ynyl)piperidine hydrogen oxalate (15). Synthesized from commercially available phenylacetylene and *N*-(3-(methylsulfonyl)propyl)piperidine. The crude product was purified through column chromatography (eluent: dichloromethane/methanol 95:5 + 0.5% aqueous NH_3). The final product was crystallized as a salt of oxalic acid from ethanol/diethyl ether, and recrystallized from ethanol (16%). ^{1}H NMR (CD_3OD) δ 1.70 (br, 2H, Pip-4H_2), 1.86 (br, 4H, Pip-3,5H_2), 1.99–2.07 (m, 2H, PipN-CH_2CH_2), 2.55–2.59 (t, J = 6.7 Hz, 2H, CH_2C≡), 3.05 (br, 2H, Pip-2,6H_a), 3.22–3.26 (m, 2H, PipN-CH_2), 3.48–3.51 (m, 2H, Pip-2,6H_e), 7.29–7.31 (m, 3H, Ph-2,4,6H), 7.36–7.39 (m, 2H, Ph-3,5H); ^{13}C NMR (CF_3COOD) δ 18.3 (≡CCH_2), 23.1 (Pip-4), 24.4 (PipN-CH_2CH_2) 25.4 (Pip-3,5), 57.0 (Pip-2,6), 59.9 (PipN-CH_2), 85.8 (PhC≡), 87.9 (Pip...C≡), 124.1 (Ph-1), 126.3 (Ph-4), 130.5 (Ph-2, 3,5,6), 162.4 (Ox); FAB$^+$-MS m/z (%) 228 (M−H$^+$, 100).

N-(5-Phenylhept-4-ynyl)piperidine hydrogen oxalate (16). Synthesized from **13b** and 1-(3-(methylsulfonyl)-propyl)piperidine. The crude product was purified through column chromatography (eluent: dichloromethane/methanol 90:10 + 1% aqueous NH_3). The final product was crystallized with oxalic acid from ethanol/diethyl ether, and recrystallized from ethanol (38%). ^{1}H NMR (CF_3COOD) δ 1.53–1.59 (m, 1H, Pip-4H_a), 1.64–1.74 (m, 2H, Pip-3,5H_a), 1.90–1.95 (m, 3H, Pip-4H_e, PipN-CH_2CH_2), 1.98–2.03 (m, 2H, Pip-3,5H_e), 2.41 (br, 2H, Pip...CH_2C≡), 2.57 (br, 2H, Ph...CH_2C≡), 2.73–2.82 (m, 2H, Pip-2,6H_a), 2.85–2.88 (t, J = 6.6 Hz, 2H, PhCH_2), 3.10–3.15 (m, 2H, PipN-CH_2), 3.48–3.51 (m, 2H, Pip-2,6H_e), 6.54 (br, 1H, NH^+), 7.26–7.30 (m, 3H, Ph-2,4,6H), 7.34–7.37 (m, 2H, Ph-3,5H); ^{13}C NMR (CF_3COOD) δ 17.5 (≡CCH_2...Pip), 21.9 (≡CCH_2...Ph), 23.0 (Pip-4), 24.3 (PipN-CH_2CH_2), 25.3 (Pip-3,5), 36.3 (PhCH_2), 56.9 (Pip-2,6), 60.6 (PipN-CH_2), 80.6 (Ph...C≡), 85.5 (Pip...C≡), 128.4 (Ph-4), 130.4 (Ph-3,5), 130.8 (Ph-2,6), 143.1 (Ph-1), 162.3 (Ox); FAB$^+$-MS m/z (%) 256 (M-H$^+$, 100).

Pharmacology

Histamine H_3-receptor antagonist potency on guinea-pig ileum. Strips of guinea-pig ileal longitudinal muscle with adhering myenteric plexus, approximately 2 cm in length and proximal to the ileocaecal junction, were prepared as previously described[26] and mounted isometrically under a tension of approximately 7.5 ± 2.0 mN in 20-mL organ baths filled with modified Krebs–Henseleit solution of the following composition (mM): NaCl 117.9, KCl 5.6, $CaCl_2$ 2.5, $MgSO_4$ 1.2, NaH_2PO_4 1.3, $NaHCO_3$ 25.0, D-glucose 5.5, and choline chloride 0.001. The solution was aerated with 95% O_2/5% CO_2 (V/V) and kept at 37 °C. Mepyramine (1 μM) was present throughout the experiment to block ileal H_1 receptors. After an equilibration period of 1 h with washings every 10 min, the preparations were stimulated for 30 min with rectangular pulses of 15 V and 0.5 ms at a frequency of 0.1 Hz. Viability of the muscle strips was monitored by addition of the histamine H_3-receptor agonist (*R*)-α-methylhistamine (100 nM), which caused a relaxation of the twitch response of more than 50% up to 100%. After wash-out, reequilibration and 30 min field-stimulation, a cumulative concentration-response curve to (*R*)-α-methylhistamine (1–1000 nM) was constructed. Subsequently, the preparations were washed intensively and reequilibrated for 20–30 min in the absence of the antagonist under study. During the incubation period the strips were stimulated continuously for 30 min. Finally, a second concentration-response curve to (*R*)-α-methylhistamine was obtained.[26,27] The rightward displacement of the curve to the histamine H_3-receptor agonist evoked by the antagonist under study was corrected with the mean shift monitored by daily control preparations in the absence of antagonist. All compounds were tested in concentrations that did not block ileal M_3 receptors (Table 1).

Histamine H_3-receptor antagonist potency in vivo in the mouse. In vivo testing was performed after oral administration to Swiss mice according to Garbarg et al.[28] Brain histaminergic neuronal activity was assessed by measuring the main metabolite of histamine, N^{τ}-methylhistamine. Mice were fasted for 24 h before po treatment. Animals were decapitated 90 min after treatment, and the cerebral cortex was isolated. The cerebral cortex was homogenized in 10 vol of ice-cold perchloric acid (0.4 M). The N^{τ}-methylhistamine level was measured by radioimmunoassay.[29] By treatment with 3 mg/kg ciproxifan the maximal increase in N^{τ}-methylhistamine level was obtained[30] and related to the level reached with the administered drug. Each experiment was performed at least in triplicate. The ED_{50} value was calculated as mean with SEM.[31]

Muscarinic M_3-receptor assay on guinea-pig ileum. The procedure was performed according to Pertz and Elz.[20]

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